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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/534,376	03/24/2000	Kari Alitalo	28967/34140A	2155

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EXAMINER
O HARA, EILEEN B

ART UNIT	PAPER NUMBER
1646	9

DATE MAILED: 02/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/534,376	ALITALO ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *2,15-18,21,22 and 24-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-14,19,20 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-39* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☒ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-39 are pending in the instant application.

Election/Restrictions

2. Applicant's election with traverse of Group A and subgroup VI, drawn to the methods of Group A using a polypeptide including residues 161-211 and lacking at least carboxyl-terminal residues of SEQ ID NO: 8 beyond residue 227 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that Groups A and B both describe a method of modulating Flt4 activity by administering a protein, and that specifically, both VEGF-C (Group A) and the antibody to VEGF-C (Group B) are proteins that modulate Flt4-expressing cells. Applicants further assert that the search based on the polypeptides of Group A indicate the uses of these polypeptides are novel and unobvious, then the use of the Group B antibodies should also be novel and non-obvious, and it should not be a serious burden on the Examiner to do one search and examination based on the claims in Group A and B, and it would be expected that a search relating to Group B will require evaluation of art relating to the antigen, since antibodies are frequently characterized in the literature only by the antigens to which they bind.

This is not found persuasive because consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof: (B) a separate status in the art when they are classifiable together: (C) a different field of search:. These criteria were met in the above restriction. A search for antibodies to a protein would constitute a different search than that of a search for the protein. It is old and well known in the art that

antibodies have been generated without having purified protein, and antibodies to one protein may also cross-react with a related protein. Additionally, antibodies to VEGF-C would be expected to have a different effect on modulation of Flt4 compared to modulation of Flt4 by VEGF-C protein, and would require different considerations during examination. As stated in the MPEP § 803, "a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP § 808.02." Further, a search is directed not only to art which would be anticipatory, but also to art that would render the invention obvious. Thus, the groups require divergent searches as well as consideration, and to search and examine both inventions would be burdensome.

Applicants further traverse the restriction of Group A (same arguments for Group B) into twelve "species". Applicants are advised that the further restriction of Group A was not a species requirement, but were drawn to different groups (subgroups). The traversal is on the grounds that subgroups I (full length sequence) and VI-IX (smaller sequences) are related in that they specify amino acid sequences from the human VEGF-C polypeptide, and because of the open language employed in the claims, each subgroup comprises a minimum recited portion of SEQ ID NO: 8, and also comprises successively larger VEGF-C polypeptide fragments that include the minimum recited portion. Applicants further assert that the "election of species" prong of the test expressed under MPEP § 806.04(b) requires that if "the claims" [are] to be restricted to different species [, the Examiner] must recite the mutually exclusive characteristics of the species." MPEP § 806.04(f), and that the Examiner has failed to identify mutually exclusive characteristics of Subgroups V-IX, and it is not clear

that the mutual exclusivity requirement of MPEP § 806.04(f) has been considered in the decision to restrict. Applicants further assert that the Examiner is required to demonstrate a different field of search for the several inventions claimed or otherwise provide support for restriction (since the classification is the same), and that the MPEP mandates that if the search and examination of the entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to independent inventions, and because of the long stretches of sequence identity between Subgroups I and V-IX, any thorough search of elected Subgroup VI will likely uncover all art related to any of the other, non-elected Subgroups. Applicants further assert that the restriction requirement is supposed to acknowledge the existence of genus claims linking alleged patentably distinct species, and upon allowance of linking claims, the restriction as to linked species must be withdrawn, and that the restriction requirement failed to contain usual acknowledgement of this standard practice, that Applicants's expectation that their generic claims are free of the prior art of record, and that the withdrawal of the restriction is appropriate for this reason as well.

Applicants' arguments have been fully considered but are not deemed persuasive. Although the different subgroups comprises a minimum recited portion of SEQ ID NO: 8, and also comprises successively larger VEGF-C polypeptide fragments that include the minimum recited portion, they are patentably distinct inventions, because the different polypeptides have different activities, properties and effects, such as differentially binding to VEGFR-3 and VEGFR-2 and having either agonistic or antagonistic effects. These different properties are the mutually exclusive characteristics that form the basis of the restriction.

Although a sequence search will likely uncover art related to the other subgroups, each of the sequences would have to be evaluated separately for examination on the merits, which would constitute a serious burden. Additionally, Applicants are advised that the further restriction of Group A was not a species requirement, but were drawn to different groups (subgroups) of patentably distinct inventions, and therefore there is no linking genus claim.

Therefore, the restriction is maintained.

Telephonic Response to New Group added to Previous Restriction

3. Upon examination of the claims, the Examiner discovered that claim 27, drawn to a method of gene therapy, had been inadvertently overlooked in the previous restriction requirement. Mr. Gass was informed of this and responded telephonically that he wanted to elect the methods of treatment with the polypeptide, which is more fully addressed in the attached interview summary.

Claims 2, 15-18, 21, 22 and 24-39 are withdrawn as being drawn to a non-elected invention.

Claims 1, 3-14, 19-20 and 23 are currently under examination.

Information Disclosure Statement

4.1 References A1-A4 have been considered but will not be published since they are applications.

4.2 Reference B17, WO 98/**49**300 was not considered because WO 98/**43**900 was submitted mistakenly in its place with the references.

4.3 The sequences disclosed in the IDS (references C8, C50-95, C98-101 and C206-207) have been looked at, but without an explanation of relevance or a sequence alignment, the relevancy of the sequences cannot be determined.

Priority

5. This application filed under former 37 CFR 1.60 lacks the current status of the nonprovisional parent applications 08/795,430, 08/858,895 and 08/510,133, which have issued as patents 6,130,071, 6,245,530 and 6,221,839, respectively. "Now U.S. Patent No. _____" should follow the application numbers in the first sentence of the specification.

Claim Objections

6.1 Claim 5 is objected to because of the following informalities: the claim includes in section (b) an antibody, which is drawn to a non-elected invention, which should be deleted. Appropriate correction is required.

6.2 Claims 1, 5, 6, 11, 12, 19 and 20 are objected to for encompassing a non-elected invention. The claims should be amended to recite the elected invention or deleted.

6.3 The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claim 19 recites hybridization conditions that are not taught in the specification. Although the claim was as originally filed and the hybridization conditions are ***not*** new matter, the specification must be amended to include those hybridization conditions. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7.1 Claims 1, 3-8, 11-14, 19, 20 and 23-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for stimulating endothelial cell growth, does not reasonably provide enablement for regulating or modulating endothelial cell growth. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The specification discloses that small fragments of VEGF-C (SEQ ID NO: 8) retain the ability to bind to and activate VEGFR-3 (also known as Flt4 receptor tyrosine kinase), and provides experiments with such truncated and/or modified VEGF-C polypeptides demonstrating this function. In the case of the elected invention, a VEGF-C polypeptide comprising amino acid

residues 161-211 of SEQ ID NO: 8 and lacking at least carboxy-terminal residues of SEQ ID NO: 8 beyond residue 227, the application teaches that this small fragment, from sequence comparisons with members of the VEGF family of polypeptides, is expected to also retain biological activity (specification at page 76, lines 8-18). The only biological activity disclosed for these fragments is stimulation or activation of the VEGFR-3 receptor, and stimulation of proliferation of endothelial cell growth. However, the claims encompass regulation or modulation of cell growth, which encompasses activities other than that of stimulation, and the specification has not provided any information that the small VEGF-C fragment will have any activity other than that of promoting cell growth, and therefore that disclosure is not enabled for the scope of the claimed invention.

7.2 Claims 5-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for stimulation of endothelial cell growth by activation of Flt4 receptor in vitro or in vivo with the small fragment of VEGF-C (VEGF-C polypeptide comprising amino acid residues 161-211 of SEQ ID NO: 8 and lacking at least carboxy-terminal residues of SEQ ID NO: 8 beyond residue 227), does not reasonably provide enablement for a method of treatment of a patient by identifying a patient in need of modulation of Flt4 activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The specification provides ample evidence and guidance for treatment of patients with VEGF-C and smaller fragments thereof, but not for identification of patients in need of modulation of Flt4 activity. The instant specification has not provided guidance as to how to determine what patient

would be in need of modulation of Flt4, and no patient population has been identified as needing modulation of Flt4, and therefore is not enabled for the scope of the invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 19, 20 and 23-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are indefinite because claim 19 is drawn to a method of modulating the activity of Flt4 receptor by transforming cells with a polynucleotide encoding a VEGF-C polypeptide, wherein the cells express and secrete the polypeptide, and then contacting Flt4-expressing cells, but there is no step wherein the polypeptide is purified before adding it to the cells, making it an incomplete method.

Conclusion

9. No claim is allowed.

The art considered pertinent to the present application is Bayne et al., PN 5,994,300, which discloses a VEGF-C protein. This reference does not teach or suggest what is being claimed, but is cited as a protein having similar activities.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Elizabeth C Kemmerer

Patent Examiner